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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,945	08/23/2005	Andrea Capocchi	263361US0PCT	4907

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EXAMINER	
HENRY, MICHAEL C	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/516,945	CAPOCCHI, ANDREA	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following office action is a responsive to the Amendment filed, 01/21/09.

The amendment filed 01/21/09 affects the application, 10/516,945 as follows:

1. The rejections made under 35 U.S.C. 103(a) are maintained.
2. The declaration of Daniela Brigheuti (not an inventor), submitted by Applicants on 02/09/09 under 37 CFR § 1.132, is acknowledged and will be further discussed below.
3. The responsive to applicants' declaration, amendments and arguments is contained herein below.

Claims 37-48 are pending in application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi et al. (EP 0153998 A2).

In claim 37, applicant claims a process of lyophilization for the preparation of a piroxicam:β-cyclodextrin inclusion compound in a 1:2.5 molar ratio conducted on a kilogram scale comprising: a) dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C;

(b) pouring the piroxicam and β-cyclodextrin dissolved in water from (a) on temperature-controlled shelves of a freeze-dryer pre-cooled to a temperature

of at least -30 °C to lower the temperature of the solution to -10 °C at a cooling rate equal to or higher than 1 °C/min, to produce a frozen solution; c) further lowering the temperature of the frozen solution to at least -20 °C; and c) drying the frozen solution under vacuum, wherein the inclusion reaction is complete with complete amorphization of the inclusion compound and complete conversion of the piroxicam to the zwitter-ionic form. Dependent claims 38-40 and 43-45 are drawn to the use of specific temperatures and cooling rates. Claims 41 and 42 are drawn to said method wherein the hot solution is specifically cooled and poured in liquid nitrogen and wherein the product is obtained in specific form. Claim 46 is drawn said method involving the use of specific % concentration and weight ratio of ammonium hydroxide to the piroxicam. Claims 47 and 48 are drawn to said method with specific time of achieving the temperature of freezing the hot solution, and wherein the process is conducted on an industrial scale.

Chiesi et al. disclose a process of lyophilization for the preparation of a piroxicam;β-cyclodextrin inclusion compound in a 1:2.5 molar ratio (0.088:0.220 moles) comprising dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and 30% ammonium hydroxide in water brought to a temperature of 60 °C; bringing the hot solution to the temperature of -20 °C of complete freezing and drying the frozen solution under vacuum (freeze drying) (see pages 3-4, example 4). It should also be noted that applicant further claims a lowering of temperature of their solution to a temperature -20 °C which is the same temperature to which Chiesi et al. lowers their solution (see applicant's, claim 37).

The difference between applicant's claimed method and the method of Chiesi et al. is that applicant freezes or cools their solution to a temperature of -10 °C then further to -20 °C whereas Chiesi et al.'s freezes or cools their solution to a temperature of -20 °C, and Chiesi et al.'s is silent about the rate of cooling or freezing rate of said solution. However, Chiesi et al.'s disclose that their solution can be freeze dried in general and thus a skilled artisan would be motivated to adjust the physical parameters used in Chiesi et al.'s method such as temperature so as to optimize the reaction conditions and/or based on factors such as availability or need. Also, even if the rate of cooling or freezing was different, the rate of cooling or freezing should not affect the product formed especially since applicant's claimed lyophilized product is the same as Chiesi et al.'s lyophilized product and since they both used the same reactants to produce their said lyophilized product.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have used the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic diseases.

One having ordinary skill in the art would have been motivated, to use the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic diseases, because a skilled artisan would reasonably be expected to adjust said parameters so as to optimize the reaction conditions and/or based on factors such as availability or need. It should be noted that a skilled artisan would be motivated to adjust the physical parameters used in Chiesi et al.'s method such as temperature, the

manner of cooling and rate of cooling the solution so as to optimize the reaction conditions and/or based on factors such as availability or need.

Response to Arguments

Applicant's arguments with respect to claim 37-48 have been considered but are not found convincing.

The Declaration under 37 CFR 1.132 filed 01/21/09 is insufficient to overcome the rejection of claims 37-48 based upon Chiesi et al. (EP 0153998 A2) as set forth in the last Office action because: Applicant's declaration pertains to demonstrating that the dissolution kinetics of the lab scale lyophilized product of Chiesi et al. is slower than that of the lyophilized product of the present invention. The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document and also fails to demonstrate that the claimed process is not obvious over the said prior art. For example, the declaration in comparing the claimed invention with Chiesi et al.'s process uses different grams of the complex (i.e., 20 grams of the applicant's complex as compared to 7.5 grams of Chiesi et al.'s complex) which shows different dissolution rates or kinetics. However, it is well known that the kinetics or rate of a reaction or dissolution of a compound or complex depends on the concentration of the reactant(s). Consequently, since a smaller amount of grams of Chiesi et al.'s complex was dissolved in the same amount of water (250 ml) (which equates to a smaller concentration of Chiesi et al.'s complex) compared to the complex of the claimed invention, one of ordinary skill in the art would reasonable expect or predict a slower dissolution rate or kinetics rate for Chiesi et al.'s complex. Also, it should be noted that Chiesi et al.'s compound which has the

same molar ratio of piroxicam:β-cyclodextrin (i.e., 1:2.5) as applicant's compound should produce the same dissolution rate or kinetics under the same conditions including the use of the same amount of grams per volume or the same concentration. Thus, the results of applicants declaration is expected or obvious over Chiesi et al.'s and also predictable.

The applicant argues that t*he Applicant has found that 'for ensuring the best performances in terms of dissolution rate [...] the manufacturing process should be able to achieve not only the completeness of the inclusion reaction but also the complete amorphization of the whole product. Moreover, since the dissolution profile is strictly dependent on the intramolecular structure assumed by piroxicam in the inclusion compound, the manufacturing process should be able to achieve the complete conversion of piroxicam in the zwitter-ionic form'* (paragraph [0015]). However, it should be noted that Chiesi et al.'s compound which has the same molar ratio of piroxicam:β-cyclodextrin (i.e., 1:2.5) as applicant's compound should also have the same intramolecular structure assumed by piroxicam in the inclusion compound and the piroxicam have should also have the same complete conversion. Furthermore, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is

the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants.

The applicant argues that Chiesi et al. are silent about the problem that could be met by passing from a lab scale to a kilogram scale, and there is nothing disclosed therein that would motivate or prompt the skilled artisan to maintain in the solid state the same structure of the inclusion complex in solution, with piroxicam in the zwitter-ionic form by strictly controlling the rate of cooling (paragraph [0039]). However, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form. It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. Thus, a skilled artisan would expect to produce the same solid state structure of the inclusion complex, regardless of the said lab scale or kilogram scale.

The applicant argues that the Examiner states that, *even if the rate of cooling is different, the rate of cooling should not affect the product formed especially since applicant's lyophilized claimed is the same as Chiesi et al. 's lyophilized product [...].* But, the Applicant respectfully disagrees with that conclusion and submits the data of the

declaration demonstrate that the dissolution kinetics of the lab scale lyophilized product of Chiesi et al. is slower than that of the lyophilized product of the present invention. However, The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document and also fails to demonstrate that the claimed process is not obvious over the said prior art. For example, the declaration in comparing the claimed invention with Chiesi et al.'s process uses different grams of the complex (i.e., 20 grams of the applicant's complex as compared to 7.5 grams of Chiesi et al.'s complex) which shows different dissolution rates or kinetics. However, it is well known that the kinetics or rate of a reaction or dissolution of a compound or complex depends on the concentration of the reactant(s). Consequently, since a smaller amount of grams of Chiesi et al.'s complex was dissolved in the same amount of water (250 ml) (which equates to a smaller concentration of Chiesi et al.'s complex) compared to the complex of the claimed invention, one of ordinary skill in the art would reasonable expect or predict a slower dissolution rate or kinetics rate for Chiesi et al.'s complex. Also, it should be noted that Chiesi et al.'s compound which has the same molar ratio of piroxicam:β-cyclodextrin (i.e., 1:2.5) as applicant's compound should produce the same dissolution rate or kinetics under the same conditions including the use of the same amount of grams per volume or the same concentration. Thus, the results of applicants declaration is expected or obvious over Chiesi et al.'s and also predictable.

The applicant argues that the Applicant respectfully observes that, if the process of Chiesi et al. is carried out on a kilogram scale, crystallization of β-cyclodextrin at 50-55 °C occurs and this occurrence does alter the characteristics of the obtained product as

residual crystalline β-cyclodextrin will be present and complete amorphization of the whole product will be no longer possible. However, whatever happens to the solution at a temperature of 50-55°C is irrelevant, is not claimed, and does not alter the fact that Chiesi et al.'s process produces a complex of piroxicam:β-cyclodextrin complex of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin at the same claimed temperature of -20°C, as claimed by applicant. In addition, Chiesi et al. disclose the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

The applicant argues that in the case of the lyophilized product of the present invention, the rate of cooling for reaching the temperature of complete freezing (-10 °C) as claimed is important in the present invention. However, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is

characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants.

The applicant argues that what it is critical is the rate of cooling for reaching the temperature of complete freezing (-10°C) while the cooling rate, and hence the time for passing from the temperature of-10°C to what of-30°C is not critical, as explained in paragraph [0049] of the specification. However, Chiesi et al. disclose the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants.

The applicant argues that the Applicant has demonstrated that the dissolution kinetics of the lab scale lyophilized product of Chiesi et al. is slower than that of the lyophilized product of the present invention. However, The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document and also fails to demonstrate that the claimed process is not obvious over the said prior art. For example, the declaration in comparing the claimed invention with Chiesi et al.'s process uses different grams of the complex (i.e., 20 grams of the applicant's complex as compared to 7.5 grams of Chiesi et al.'s complex) which shows different dissolution rates or kinetics. However, it is well known that the kinetics or rate of a reaction or dissolution of a compound or complex depends on the concentration of the reactant(s). Consequently, since a smaller amount of grams of Chiesi et al.'s complex was dissolved in the same amount of water (250 ml) (which equates to a smaller concentration of Chiesi et al.'s complex) compared to the complex of the claimed invention, one of ordinary skill in the art would reasonable expect or predict a slower dissolution rate or kinetics rate for Chiesi et al.'s complex. Also, it should be noted that Chiesi et al.'s compound which has the same molar ratio of piroxicam:β-cyclodextrin (i.e., 1:2.5) as applicant's compound should produce the same dissolution rate or kinetics under the same conditions including the use of the same amount of grams per volume or the same concentration. Thus, the results of applicants declaration is expected or obvious over Chiesi et al.'s and also predictable.

The applicant argues that it is also the Applicant's belief that the data disclosed in the Scappaticci Declaration clearly demonstrated that, by applying the teaching of Chiesi

et al. on a kilogram scale, it is not possible to obtain a lyophilized product with all the characteristics of the lyophilized product of the present invention, as residual crystalline β-cyclodextrin will be present and complete amorphization will be no longer possible. However, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. It should also be noted that the Scappaticci Declaration was discussed by the examiner in the prior office action.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
April 11, 2009.

/Shaojia Anna Jiang/
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